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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
UNGAR, SUSAN NMN	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/966,147	PRESTA ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *28 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,4-7 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,4-7 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/21/04,10/16/02*. 9/27/01
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S 00.

1. The Amendment filed June 28, 2005 in response to the Office Action of March 28, 2005 is acknowledged and has been entered. Previously pending claims 1 and 23 have been amended. Claims 1, 4-7, 23 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Applicant's reiteration of request for priority to March 18, 1994 is acknowledged. Applicant argues that the full-length trkC sequence of SEQ ID NO:6 is found in the priority application SN 08/215,139 filed March 18, 1994 and the use of TrkC antibodies for the treatment of axonal sprouting in epilepsy is also mentioned at page 88, lines 6-7. The request and arguments have been considered but have not been found persuasive as Applicant is arguing limitations not recited in the claims as currently constituted, the claims are not drawn to the use of trkC antibodies for the treatment of axonal sprouting in epilepsy. The priority date for the instantly claimed invention remains at August 5, 1994.

4. The following rejections are being maintained:

Claim Rejections - 35 USC 112

5. Claims 1, 4-7, 23 remain rejected under 35 USC 112, first paragraph for the reasons set forth previously in the Paper mailed March 28, 2005, Section 5, pages 2-8.

Applicant argues that the claims as currently amended are explicitly directed to inhibiting the activity of full-length trkC receptors and since a trkC receptor without activity, such as a "non-productive receptor" or an inactive truncated or variant form, would not be inhibited being already inactive, the concerns related to truncated or variant forms, forms arising by alternate splicing or non-productive receptors are believed to be moot in view of the present claims directed to

inhibiting the activity of the full-length trkC receptor of SEQ ID NO:6. The argument has been considered but has not been found persuasive because even if a nexus were to be established between treatment of aberrant neuron sprouting and inhibition of the activity of SEQ ID NO:6, the amendment to the claims does not address the issue raised drawn to the effects of binding of the inhibitory antibody to truncated or variant forms, forms arising by alternate splicing or non-productive receptors on the function of the instant invention. The specification provides no teaching or guidance drawn to the non-productive receptors and their sequestration of the antagonist antibody and given that sequestration and the lack of teaching in the specification, it cannot be predicted whether sufficient antibody would bind human trkC receptor of SEQ ID NO:6 to function as claimed. The specification provides no information as to which epitopes are selective for the full length receptor compared to the truncated or variant forms of the receptor. In the absence of this guidance, one would not know how to predictably distinguish between antagonist antibody that would selectively antagonize the activity of SEQ ID NO:6 and therefore would not be sequestered by truncated or variant forms of the receptor and thus would function as claimed. Given the above it could not be predicted that sufficient antagonist antibody would reach to a human trkC receptor of SEQ ID NO:6 to function as claimed. Although the claims are drawn to antibody binding that inhibits the activity of said trkC receptor, given the inadequate teaching in the specification, the newly added limitation does not teach how to make and use the invention for the reasons set forth above.

Applicant reiterates arguments drawn to the art recognizing an association between neuronal sprouting and epilepsy and recognizing a relationship between

trkC, NT-3, neuronal sprouting and epilepsy. The arguments were previously considered and were not found convincing for the reasons of record.

Applicant argues that the specification directly and explicitly discloses that the invention is useful in treating epilepsy. The argument has been considered but has not been found persuasive because Applicant is arguing limitations not recited in the claims as currently constituted.

Applicant argues that it was recognized in the art that aberrant sprouting was related to epilepsy and that aberrant sprouting might be affected by neurotrophin levels and neurotrophin receptor activity and given the disclosure in the specification, one of skill would immediately recognize and appreciate the connection between inhibition of the activity of a trkC receptor of SEQ ID NO:6 and the treatment of epilepsy and thus a nexus is established and would have been recognized as such by one of ordinary skill in the art. This reiterated argument was considered previously and was not been found persuasive for the reasons of record. Further, Applicant is arguing limitations not recited in the claims as currently constituted since the claims are not drawn to aberrant sprouting in epilepsy.

Applicant argues that the Hongo Declaration, dated March 1, 2002 specifically teaches that "molecules that antagonize neurotrophin or Trk activity find use in the treatment of diseases characterized by neurotrophin or Trk receptor expression as determined by mRNA or protein assessment" and therefore the mRNA data presented in Bengzon is relevant to the instant invention and may be relied upon to provide a nexus between trkC, SEQ ID NO:6, protein antagonism, NT3, neuron sprouting and epilepsy. The argument has been considered but has not been found persuasive because once again, Applicant is arguing limitations not recited in the claims as currently constituted. Further, the data presented in the

Hongo Declaration is not drawn to RNA, but rather is drawn to protein assays to determine the effects of antagonist antibodies on TrkC binding and activity and it is not clear from the Declaration why the statement drawn to mRNA is made because no evidence is presented that demonstrates a reliable correlation between mRNA and protein overexpression of TrkC, SEQ ID NO:6. Although it appears that Dr. Hongo is suggesting that there is a correlation between mRNA and protein expression of TrkC, in particular, and solely in response to Applicant's arguments and the teaching of the Hongo Declaration, Examiner takes notes that the literature is replete with evidence that, protein levels do not predictably correlate with steady-state mRNA levels or alterations in mRNA levels. For instance, Brennan et al (Journal of Autoimmunity, 1989, vol. 2 suppl., pp. 177-186) teach that high levels of the mRNA for TNF alpha were produced in synovial cells, but that levels of the TNF alpha protein were undetectable. Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and the protein level, indicating that S100 protein is post-transcriptionally regulated. Eriksson et al (Diabetologia, 1992, vol. 35, pp. 143-147) teach that no correlation was observed between the level of mRNA transcript from the insulin-responsive glucose transporter gene and the protein encoded thereby. Powell et al (Pharmacogenesis, 1998, Vol. 8, pp. 411-421) teach that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding protein, and conclude that the regulation of said protein is highly complex. Carrere et al (Gut, 1999, vol. 44, pp. 55-551) teach an absence of correlation between protein and mRNA levels for the Reg protein. Vallejo et al (Biochimie, 2000, vol. 82, pp. 1129-1133) teach that no correlation was found between NRF-2 mRNA and protein levels suggesting post-

transcriptional regulation of NRF-2 protein levels. Guo et al (Journal of Pharmacology and Experimental Therapeutics, 2002, vol. 300, pp. 206-212) teach that Oatp2 mRNA levels did not show a correlation with Oatp2 protein levels, suggesting that regulation of the Oatp2 protein occurs at both the transcriptional and post-translational level. These references serve to demonstrate that levels of polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression. Thus in the absence of objective evidence that there is a reliable correlation between mRNA levels and protein levels of trkC, the Bengzon et al reference is not commensurate in scope with the claimed invention and is not relevant to this rejection.

Applicant argues that McNamara's conclusion that trkC may be involved in pathologic morphologic rearrangements enables the claimed invention and Applicant disagrees with Examiner's finding that given this statement and the other teachings of McNamara that the art did not recognize a predictable nexus between trkC, NT3 and neuronal sprouting. The argument has been considered but has not been found persuasive given the use of the term "may". Clearly it was unknown to McNamara at the time the reference was published that trkC was involved in pathologic morphologic rearrangements and given that it was unknown, given the hypothetical nature of the statement, given the teaching of the other references, it is clear that based on the teachings of McNamara, one would not know how to use the claimed invention. Further it is noted that, as again drawn to McNamara, Applicant neglects to address the issue raised drawn to the heterogeneity of epilepsies and the lack of teaching in the specification as to how to determine the patient population that would predictably benefit from the instantly claimed

method. The arguments have been considered but have not been found persuasive and the rejection is maintained.

Applicant reiterates arguments drawn to the Declaration of Hongo and specifically reiterates that "Trk-specific antibodies...find use in the treatment of diseases characterized by neurotrophin or Trk receptor expression....." apparently indicating that the Hongo Declaration enables the claimed invention. However, only in response to the newly discussed Hongo Declaration, Examiner finds that the information in the Hongo Declaration does not enable the claimed invention because the data presented is not commensurate in scope with the claimed invention. The claimed invention is drawn to the inhibition of aberrant neuron sprouting *in vivo* and the data presented is drawn to *in vitro* data wherein cell lines overexpressing TrkC receptors were assayed for NT-3 binding inhibition by antagonist antibodies and were assayed for NT-3-dependent receptor phosphorylation inhibition by antagonist antibodies. In particular, as drawn to cell culture studies and only in answer to Applicant's reference to the Hongo Declaration in the Response to the claim rejections, one cannot extrapolate the teaching of the Declaration to the enablement of the claims because Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may

not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "when a normal ..... body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal ..... cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years". Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Further, in the assays, the antagonist is in contact with cells during the entire exposure period. This is not the case *in vivo*, where exposure at the target site may be delayed or inadequate. In addition, as previously set forth, variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The antibody may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life and the *in vitro* tests of record do not sufficiently duplicate the conditions which occur *in vivo*. In addition, the antibody may not otherwise reach the target because it may be absorbed by fluids, cells and tissues where the antibody has no effect. This is particularly critical here given the non-productive receptors, variants, truncated forms of TrkC which would be expected to sequester the claimed antagonist antibody. The specification provides insufficient guidance with regard to theses

issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed inventions with a reasonable expectation of success. It is noted that the issues remain the same, the claimed invention is not enabled for the reasons of record.

5. Claims 1, 4-7, 23 remain rejected under 35 USC 112, first paragraph for the reasons set forth previously in the Paper mailed March 28, 2005, Section 6, pages 8-9, July 23, 2004, section 5, pages 5-6 and January 15, 2004, Section 10, pages 11-15.

Applicant argues that since the claims are directed to methods using antibodies that specifically bind the full length trkC receptor and inhibit its activity, the specification provides adequate written description. The argument has been considered but has not been found persuasive because the written description rejection is not drawn to the claimed antibodies. The written description rejection made and consistently maintained since January 15, 2004 is drawn to the lack of description of the population associated with aberrant neuron sprouting since the only teaching in the specification drawn to the instant invention is that "antagonists of trkC are thought to be useful to treat aberrant neuron sprouting in epilepsy." As previously set forth, this does not provide a written description of the population of cells to be treated for the reasons of record. Further, although Examiner responded, in the paper mailed July 23, 2004, to Applicant's arguments drawn to the written description of the population of cells rejection submitted May 13, 2004 and Examiner also responded, in the paper mailed March 28, 2005, to arguments to

the maintained written description rejection (which arguments were submitted December 21, 2004) wherein said arguments were not drawn to the population of cells, but rather to the antagonistic antibodies, the rejection drawn to the written description of the population of cells was never withdrawn and is still standing. Because Applicant has not addressed the issue raised drawn to population of cells, the rejection is maintained.

Applicant's arguments have been considered but have not been found persuasive to overcome the rejection of record and the rejection is maintained.

6. All other objections and rejections recited in the Paper mailed March 28, 2005 are hereby withdrawn.

7. No claims allowed.

8. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is

(571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
August 18, 2005